Lateral Organization in Lipid Bilayers: Atomistic and Coarse-Grained Simulations

H. Larry Scott
Department of Biological, Chemical, and Physical Sciences,
Illinois Institute of Technology, Chicago, IL, 60616

Introduction

The effect of Cholesterol on the lateral organization of multi-component membranes is a topic of high interest in membrane biophysics. An increasing number of experiments have demonstrated the existence of sphingolipid- and Cholesterol- enriched nanometer sized domains known as "functional rafts" in the plasma and possibly other membranes of animal cells.[1–3] Edidin.[4] has published a comprehensive and critical review of data from model and biological membranes that relate to domain formation and functional rafts.

Current interpretation of experimental data suggest that raft domains are small, perhaps as small as a few tens or hundreds of lipids.[4] Given the heterogeneous an dynamical composition of biomembranes, there is also some skepticism regarding the existence and functional significance of rafts.[5] *Simulation is one tool that can examine the interactions involved in atomic detail, and thereby help to resolve the issue.* For this reason our group has done simulations of phospholipid-cholesterol (Chol) mixtures,[6,7] sphingomyelin (SM)[8] and between SM and Chol.[11–13] In the following sections we present results , firstly of our MD simulations and, secondly, some new larger-scale modeling based on the Time-Dependent Ginzburg-Landau method.[15]

MD Simulations

Our most recent MD simulations were have been carried out on three different systems: (i) a ternary mixture of dioleylphosphatidylcholine (DOPC), SM, and Chol with a 1:1:1 composition, (ii) a binary mixture of DOPC/SM with a 1:1 composition which serves as a control for (i), and (iii) a ternary mixture of DOPC/SM/Chol with a 4:1:1 composition. All simulations were performed using the GROMACS package[14]. Details of the methodology and the forcefields have been described elsewhere[8,12]. The initial configurations for systems (i - iii) were generated by random placement of DOPC, SM and Chol molecules.

Our longest running ternary mixture simulation consists of 100 DOPC, 100 SM, and 100 Chol molecules plus 9600 waters. We have to date run this system for 200 ns plus 50 ns of equilibration, with the goal of determining the structural and dynamical parameters that drive the formation of domains. As a control, we have also run a simulation of a binary system consisting of 100 SM plus 100 DOPC, with no Chol. Figure 1 shows snapshots of the ternary system at 0ns, 150 ns, and 200 ns, plus a 200 ns snapshot of the binary system. We have performed the same suite of structural calculations on the random mixtures as we did on a single-domain simulation published earlier.[12] One of the important findings of this work, revealed in quantitative analysis of lateral molecular area correlations is that, on the 200 ns timescale, the presence of Chol strongly enhances the formation of segregated domains rich in either SM or DOPC.

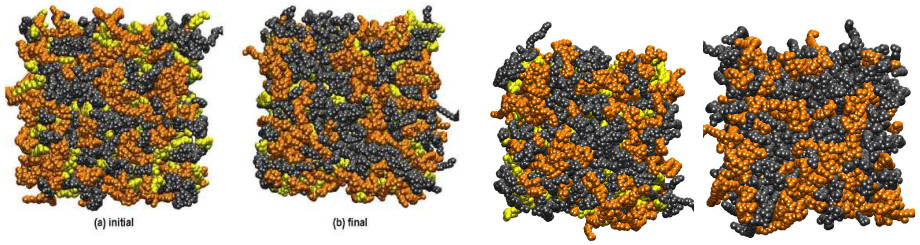

Figure 1. Snapshots of ternary DOPC-SM-Chol left: initial states (after 4 ns of equilibration). next right: after 150 ns, third right: after 200 ns; far right: binary system after 200 ns. Color code is: Black: DOPC, orange: SM, yellow: Chol.

After a more detailed analysis of Chol-SM and Chol-DOPC interactions and pair correlation functions, we have found , on this timescale, that the rough methylated face of Chol is preferentially oriented towards DOPC molecules, while the smooth face is preferentially orientated towards SM molecules. Figure 2 shows two-dimensional pair correlation function between Chol and SM, with the orientation of the Chol taken into account. The color coding shows a clear preference of SM for the smooth face of Chol. By default a similar calculation for DOPC-Chol shows a slight preponderance of DOPC nearer to the rough face of Chol molecules.

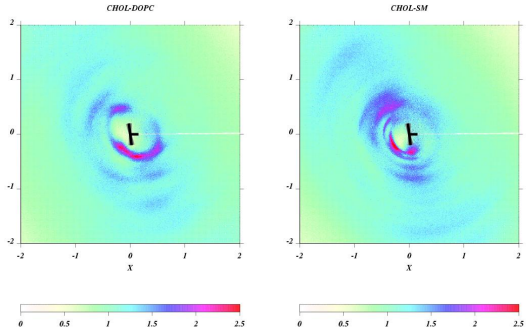

Figure 2: Density plot of $g(r, \phi)$ on the XY plane of the Chol body coordinate system at 200 ns. A top view of the Chol molecule reference frame is schematically shown as black T. The pair correlation function was calculated between O atoms of Chol and the backbone CH_1 moiety of SM (and also DOPC). Left: DOPC-Chol; right: SM-Chol

The 4:1:1 simulation consists of 200 DOPC, 50 SM, and 50 Chol. The extra DOPC in the system makes it more realistic, but also dilutes the SM and Chol so that longer simulations will be required to allow for the greater diffusive movement of the molecules necessary to form small domains. We are currently running MD on one cluster in the Scott lab for this system, and have accumulated 100 ns.

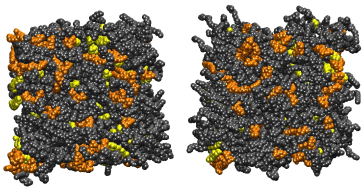

Figure 3. Snapshot of top view of 4:1:1 DOPC:SM:Chol bilayer: left, initial state, right, after 75 ns. Color code: black:DOPC, orange:SM, yellow:Chol.

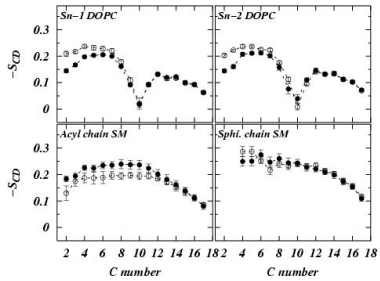

Figure 4 Order parameter profiles for DOPC and SM chains for 4-1-1 simulation at $t = 0$ (open symbols) and $t = 75$ (filled symbols) ns.

Time-Dependent Ginzburg-Landau simulations

Our coarse-grained modeling is based on a Ginzburg-Landau approach to the study of coexisting phases.[15] The remainder of my talk will focus on this unpublished work.

References

[1] K. Simons and E. Ikonen, "Functional Rafts in Cell Membranes", *Nature* 387, (1997) 569-572.

[2] Brown, D. A. and E. London. Functions of Lipid Rafts in Biological Membranes Annu. Rev. Cell. Dev. Biol. 14: (1998) 111-136.

[3] Brown, R. E. Sphingolipid Organization in Membranes: What Physical Studies of Model Membranes Reveal. J. Cell Sci. 111:(1998) 1-9.

[4] M. Edidin, "The State of Lipid Rafts: from Model Membranes to Cells" 2003 Annu. Rev. Biophys. Biomol. Struct. 32: 257-283.

[5] T. McMullen, R. Lewis, and R. McElhaney, "Cholesterol-phospholipid interactions, the liquid-ordered phase and lipid rafts in model and biological membranes", *Curr. Op. Coll. Int. Sci.* 8 (2004), 459-468.

[6] Chiu, S.-W., Jakobsson, E., Mashl, R. J., and Scott, H. L. Cholesterolinduced modifications in lipid bilayers: A simulation study. *Biophys. J.*, 83(2002):18421853.

[7] H. L. Scott, "Modeling the lipid component of membranes", *Curr. Op. Struct. Biol.* 12, (2002) 495-503.

[8] S. W. Chiu, E. Jakobsson, S. Vasudevan, R. J. Mashl, and H. L. Scott. "Structure of Sphingomyelin Bilayers: a Simulation Study". *Biophys J.* 85, (2003) 3624-3635.

[9] E. Mombelli, R. Morris, W. Taylor, and F. Fraternali. " Hydrogen Bonding Propensities of Sphingomyelin in Solution and in a Bilayer Assembly; A molecular dynamics Study". Biophys. J. 84: (2003), 1507-1517.

[10] M. Hyvönen and P. T. Kovanen, "Molecular Dynamics simulation of sphingomyelin bilayer", *J Phys. Chem. B* 107 (2003), 9102-9108.

[11] G. Khelashvili and H. L. Scott, 2004. Combined Monte Carlo and molecular dynamics simulation of hydrated 18:0 sphingomyelin - Cholesterol lipid bilayers, *J. Chem. Phys* 120, 9841-9847

[12] S. A. Pandit, S. Vasudevan, S. W. Chiu, E. Jakobsson, R. J. Mashl, and H. L. Scott. "Sphingomyelin-Cholesterol domains in phospholipid membranes", *Biophys. J.* 87 August 2004.

[13] S. Pandit, E. Jakobsson, and H. L. Scott, Simulation of early stages of domain formation in mixed bilayers of sphingomyelin, Cholesterol and dioleylposphatidylCholine, 2004. *Biophys J.*. submitted

[14] E. Lindahl, B. Hess, and D. van der Spoel, J. Mol. Mod. **7**, 306 (2001), (www.gromacs.org)

[15] T. Lubensky and P. Chaikin; *Principles of Condensed Matter Physics*, Cambridge University Press (1995).